The Microenvironment

March 2014

THE CANADIAN HEMATOLOGY SOCIETY

SOCIÉTÉ CANADIENNE D'HÉMATOLOGIE

C H S C H

NEWSLETTER

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2013 CHS Executive Committee

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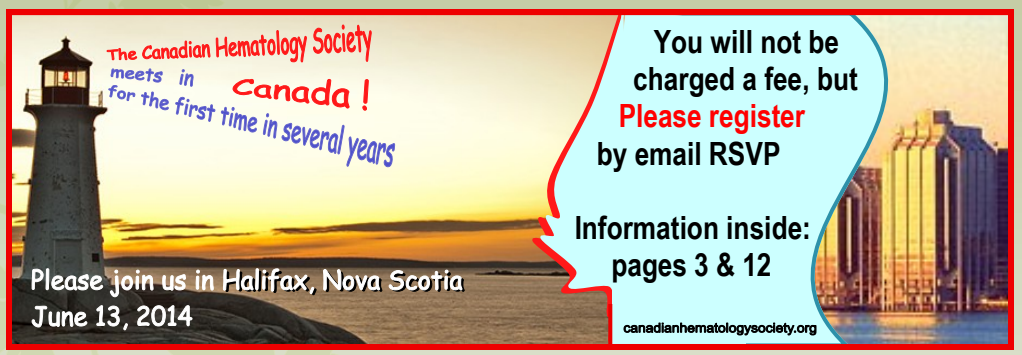

MESSAGE FROM THE PRESIDENT

Support of trainees and junior faculty, remains a top priority

Dr. Aaron Schimmer
President, Canadian Hematology Society

The past presidents of the Canadian Hematology Society (CHS) include many Canadian hematology giants and I am privileged and humbled to follow in their footsteps as I assume the presidency of the CHS.

First, I would like to thank our out-going president, **Dr. Stephen Couban**, for his hard work and contributions to the CHS. Under Stephen's leadership, the CHS has embarked on a number of new and exciting initiatives including re-establishing a Canadian hematology meeting that will occur in June 2014 and initiating a bid to host the 2018 meeting of the International Hematology Society (ISH) in Vancouver. I look forward to working with Stephen to bring these events to fruition.

I would also like to extend a warm welcome to **Dr. Lynne Savoie** who is our in-coming Vice President. I am grateful that **Dr. Molly Warner** continues to serve as our treasurer and secretary and **Dr. Tom Nevill** continues as the editor of the Microenvironment newsletter.

Dr. Gail Rock remains a linchpin in the Society in her role as Executive Vice President. I am thankful for the all of time and effort our executive members devote to the CHS. We are also fortunate to have Jean and Lisa in our CHS head office. Along with Dr. Rock, they are the glue that holds the Society together and keeps us moving forward.

Over the next several months, the CHS will make a formal bid to host the **2018 ISH** meeting in Vancouver. The bid process is being spearheaded by Drs. Nevill and Rock and early feedback from the ISH selection committee is encouraging. Hosting ISH will be a significant honor and provide an opportunity to highlight the great hematology research being conducted in this country.

Canada will also be hosting other major international hematology meetings in the next few years. For example, the ***International Society for Hematology and Stem Cells*** will be held in Montreal in August of 2014 and the ***International Society for Thrombosis and Hemostasis***

continued, page 2 →

will take place in Toronto in 2015.

Canadian hematologists are leading the organization of these meetings. In this issue of the Microenvironment, you can read more about these conferences and the roles of our CHS members in organizing these meetings. **If you are organizing similar meetings of potential interest to Canadian hematologists, you are encouraged to send us notices.**

Supporting research by hematology trainees and junior faculty remains a priority of the CHS. We continue to provide research **awards** related to abstracts presented at ASH. In addition, we offer small research grants in the form of the **R.K. Smiley awards**.

With grant funding becoming ever tighter, we hope this funding will support exciting and important Canadian hematology research.

In the 2014 competition, we received 25 applications spanning the breadth of hematology, including benign, malignant, and laboratory hematology.

We received applications related to clinical, translational and fundamental hematology research. The review of these applications is underway and the award recipients will be featured in the next edition of the newsletter.

Over the next two years, we will also embark on new initiatives to promote Canadian hematology research and details will be forthcoming in the future editions of the Microenvironment.

In February, I had the opportunity to represent the CHS at the **National Employment Summit** organized by the Royal College Physicians and Surgeons of Canada.

This meeting addressed issues of physician human resources and physician underemployment with the long-term goal of optimally aligning physician resources to ensure an adequate supply and distribution of physicians to meet the needs of our country in a fiscally responsible manner.

It became clear through this meeting that achieving this goal will require an understanding of the current and future needs of physician resources in Canada. It was also evident that the national specialty societies, such as the CHS, will have a critical role to play in this process.

For example, I think the CHS can play a leading role in collecting and communicating available hematology practice opportunities in the country. Identifying open hematology positions in Canada, is an important step to determine hematology resources and needs in the country.

These data, along with population trends and projections, will help address the question of how many hematologists do we need and where are they needed. Over the next few months, we will begin the process to collect this information.

We will be asking you to help identify open hematology practice opportunities in your community and hospital. Your response is critical for our new hematology colleagues who are starting their careers.

I hear frequently about the anxiety among current and prospective hematology trainees who are concerned about career opportunities upon completion of training. By helping us identify and communicate open hematology positions, you will be offering tremendous assistance to our new hematology colleagues.

In addition, highlighting open hematology positions and fellowship opportunities will also help recruit the best and brightest medical students and internal medicine residents to our field.

In closing, I would like to thank you for your continued commitment to the CHS and the hematology community in Canada.

Your membership dues sustain the educational and research activities of the Society and allow CHS to be a hub for hematology in the country. For those who may not be members yet, I would encourage you to visit our website (www.canadianhematologysociety.org) and learn more about the benefits of membership.

However, membership dues alone do not cover the full operating costs, and we are very grateful for our Gold, Silver and Bronze industry partners.

You will see their logos and names in the Microenvironment. When you meet the representatives of these companies, I ask you to thank them for their support of the CHS.

2014 CHS EXECUTIVE BOARD

President

Dr. Aaron Schimmer

Past-President

Dr. Stephen Couban

Vice-President

Dr. Lynn Savoie

Secretary Treasurer

Dr. Margaret Warner

Executive Vice-President

Dr. Gail Rock

Welcome ! CHS meets in June 2014 in Halifax

NOVA SCOTIA

Dear Colleagues,

As announced at the CHS Reception at ASH, many of you will know that the CHS and the Canadian Blood and Marrow Transplant Group (CBMTG) are hosting a combined symposium in Halifax on Friday June 13, 2014. I sincerely hope you will consider attending!

Years ago until 1999, Canadian hematologists gathered together in Canada during the Royal College meeting to present data and discuss issues of relevance. Then, for eight years the CHS very successfully organized an annual symposium in conjunction with a previous CBMTG or other subspecialty groups.

This year, after an eight year hiatus, I am very pleased to announce that we are again planning a Canadian hematology meeting in Canada. In addition to the CBMTG and CHS, a number of other Canadian hematology groups are meeting in Halifax on June 13, 2014 including the Canadian Apheresis Group (CAG), VECTOR (a group of hematologists with interest in research in thrombosis) and the CNTRP (a research group of clinicians and scientists from the solid organ and BMT fields).

At both the CHS and CBMTG, we welcome you to this meeting and hope that that this meeting will become a new Canadian tradition!

Please join us and have the members of your teams, including your trainees join us as well!

Stephen Couban, Chair

Scientific Organizing Committee

Friday June 13, 2014
9:00 am to 3:45 pm
The Westin Nova Scotian—Halifax, NS

PROGRAM

8:45—9:00 am *Welcome*

9:00—10:00 am Dr. Neal Young
The Diagnosis and Treatment of Severe Aplastic Anemia

10:00—11:00 am Dr. Sudeep Shivakumar & Dr. Marc Carrier
Thrombosis Challenges in Patients with Hematologic Malignancies

11 am—noon Dr. Danièle Marceau
Paroxysmal Nocturnal Hemoglobinuria

2:30 pm —3:15 pm Dr. Paul Moorehead
Hemophilia treatment: "In the Clinic and In the Future"

3:15 pm—3:45 pm Dr. Eiad Kahwash
Single Unit Transfusion

Registration Details, Page 12

Message du Président

L'appui pour la recherche des stagiaires en hématologie et la faculté junior, reste une haute priorité

Les anciens présidents de la Société canadienne d'hématologie (SCH) inclus plusieurs géants d'hématologie et je suis privilégié et humble de suivre dans leurs pas en assumant la présidence de la SCH. Premièrement, j'aimerais remercier notre président départant, Dr. Stephen Couban, pour son travail et ses contributions à la SCH.

Sous la dirigeance de Stephen, la SCH s'est embarquée sur un nombre d'initiatives nouveaux et excitants incluant le rétablissement de la rencontre annuelle d'hématologie qui va avoir lieu en Juin 2014 ainsi que l'initiation d'une proposition pour accueillir la rencontre de la Société internationale d'hématologie à Vancouver en 2018. J'espère travailler avec Stephen pour continuer le progrès sur ces évènements.

J'aimerais aussi faire un accueil chaleureux à Dr. Lynne Savoie qui est maintenant notre nouvelle vice-présidente. Je suis reconnaissant que Dr. Molly Warner continue de servir comme trésorière et secrétaire et Dr. Tom Nevill qui continue comme éditeur de la publication Microenvironnement.

Dr. Gail Rock continue comme pivot dans la société dans son rôle de vice-présidente exécutive. Je suis reconnaissant pour tout le temps et l'effort que nos membres exécutifs dévouent à la SCH. De plus, nous sommes chanceux d'avoir Jean et Lisa au bureau de la SCH. Travaillant avec Dr. Rock, elles gardent la société ensemble et aident à continuer le cheminement en avant.

Pendant les prochains mois, la SCH va soumettre une proposition formelle pour accueillir la rencontre de la Société internationale d'hématologie (SIH) à Vancouver, en 2018. Dr. Nevill et Dr. Rock sont en tête du processus de soumission et la rétroaction du comité de sélection est encourageante. Accueillir la SIH sera un grand honneur et va fournir une opportunité de surligner la recherche formidable qui se déroule dans ce pays.

Le Canada va aussi accueillir d'autres majeurs rencontres internationales d'hématologie dans les prochaines années. Par exemple, la rencontre de la Société internationale d'hématologie et Cellules souches sera à Montréal en Août 2014 et la Société internationale de thrombose et hémostase aura sa rencontre à Toronto en 2015. Certains hématologues seront en tête de l'organisation de ces rencontres.

Vous pouvez en lire plus sur ces conférences, ainsi que sur le rôle que nos membres de la SCH ont dans leur organisation, dans cette publication du Microenvironnement. Si vous organisez des rencontres semblables, d'intérêt potentiel aux hématologues Canadiens, vous êtes encouragés de nous contacter.

L'appui pour la recherche des stagiaires en hématologie et la faculté junior, reste une haute priorité pour la Société canadienne d'hématologie.

Nous continuons de fournir des prix de recherches reliés aux sommaires présentés à ASH. De plus, nous offrons des petites bourses de recherches R. K. Smiley. Avec des bourses de recherches de plus en plus difficile à obtenir, nous espérons que ces bourses fourniront des recherches importantes dans le domaine d'hématologie au Canada. Dans la compétition en 2014, nous avons reçu 25 applications étendue largement dans l'hématologie, incluant l'hématologie, bénin, malin et laboratoire. Nous avons reçu des applications reliées à la recherche hématologique clinique, translative et fondamentale. La revue de ces applications est en marche et les lauréats seront inclus dans la prochaine édition de la publication. Pendant les prochains 2 ans, nous allons aussi embarquer sur des nouvelles initiatives pour promouvoir la recherche hématologique Canadienne et plus de détails se-

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ront disponibles dans des publications futures du Microenvironnement.

En février, j'ai eu l'occasion de représenter la SCH au Sommet national sur l'emploi des médecins organisé par le Collège royal des médecins et chirurgiens du Canada.

Cette rencontre a adressé la question des ressources humaines et sous-emploi de médecins et avait comme bût d'aligner, à long terme, les ressources de médecins pour s'assurer une provision adéquate et la distribution de médecins pour rencontrer les besoins de notre pays avec une bonne responsabilité fiscale.

C'est devenue clair à la rencontre qu'obtenir ce bût va nécessiter une compréhension des besoins immédiats et futurs des ressources de médecins au Canada. C'était aussi évident pendant cette rencontre que les sociétés spéciales nationales, tel que la SCH, va avoir un rôle important à jouer dans ce processus. Par exemple, je crois que la SCH peut jouer un rôle principal à collectionner et communiquer des opportunités d'emplois en hématologie dans le pays.

Un pas important pour déterminer les ressources et besoins hématologiques dans le pays est d'identifier des positions ouvertes de positions en hématologie. Ces données, ainsi que des statistiques de population et des projections, vont aider à adresser la question de combien d'hématologistes que l'on a besoin et où on en a de besoin.

Aaron Schimmer
Président SCH

Au courant des prochains quelques mois, nous allons commencer le processus de collectionner cette information. Nous allons vous demander de nous aider à identifier des emplois ouverts en hématologie dans votre communauté et vos hôpitaux.

Votre réponse sera critique pour nos nouveaux collègues en hématologie qui débutent leurs carrières. J'entends fréquemment à propos de l'anxiété auprès des stagiaires en hématologies, courants et prospectifs, qui sont inquiet à propos de leurs possibilités d'emplois après la complétion de leurs stages.

En nous aidant à identifier et communiquer des positions ouvertes en hématologie, vous allez offrir énormément d'assistance à nos collègues en hématologie. De plus, surligner les positions ouvertes en hématologie et les opportunités postdoctoraux va aussi aider à recruter les meilleurs étudiants en médecine et résidents de médecine interne à notre domaine.

Pour conclure, j'aimerais vous remercier pour votre support continu de la SCH et la communauté d'hématologie au Canada.

Vos cotisations soutien les activités éducatives et de recherche de la société et permet à la SCH d'être le pivot pour l'hématologie au pays. Pour ceux qui ne sont pas encore membre, je vous encourage à visiter notre site web (www.canadianhematologysociety.org) pour apprendre à propos des avantages de devenir membre.

Cependant, les cotisations elles-mêmes ne couvrent pas tous les coûts d'opérations, et nous sommes très reconnaissants pour les associations partenaires au niveaux Or, Argent, et Bronze. Vous allez voir leurs logos et noms dans le Microenvironnement. Lorsque vous rencontrez les représentants de ces organisations, je vous demande de les remercier pour leur support de la SCH.

Aaron Schimmer, Président

Do you know the diagnosis?

A 23-year-old woman presented with a 2-week history progressive abdominal and lower extremity swelling with associated fatigue and an 8 kg weight loss.

- A CBC showed a hemoglobin of 62 g/L, a WBC of 16.5 x 10^9/L and platelets of 70 x 10^9/L.
- Chemistry revealed: potassium of 3.2 mmol/L, normal serum creatinine of 95 umol/L, uric acid 450 umol/L (upper normal 360), alkaline phosphatase of 643 U/L (upper normal 125), GGT 400 U/L (upper normal 65), total/direct bilirubin of 84/60 umol/L and an LDH of 260 U/L (upper normal 240).
- CT scan showed extensive lymphadenopathy in the neck, axillae, mediastinum, mesentery and pelvis as well as hepatosplenomegaly, marked ascites and peritoneal seeding.
- Peripheral blood and bone marrow examinations are shown in Figures 1 and 2, respectively.

Do you know the diagnosis?
… SEE PAGE 14

Figure 1

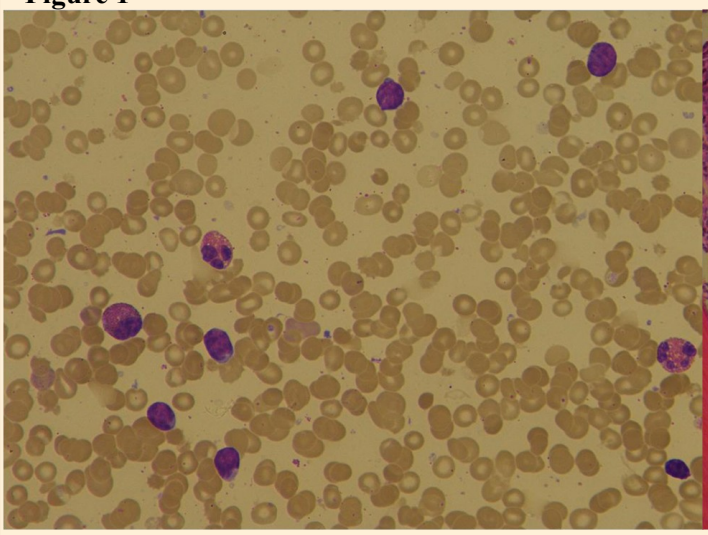
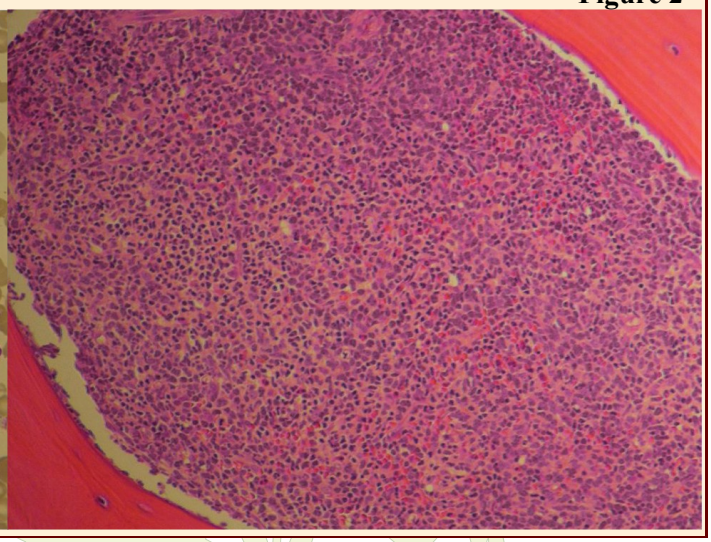


Figure 2



CHS 2013 RESEARCH AWARD WINNERS

Residents & Fellows Category - and Winner of the John H. Crookston Award

Leukemic engraftment in NOD.SCID mice is correlated with clinical parameters and predicts outcome in human AML

- **Dr. James Kennedy**
- **University of Toronto**
- **Supervisor: Dr. Jean Wang**

NOD.SCID xenotranspantation assays are a powerful tool for studying the biology of acute myeloid leukemia (AML).

The investigators transplanted peripheral blood or bone marrow cells from 307 AML patients into sublethally irradiated NOD.SCID mice and were able to achieve myeloid engraftment in 134 cases (44%).

This included 40% of samples taken at AML diagnosis and 66% of samples taken at AML relapse although only 2 patients failed to generate a graft at diagnosis but did generate a graft at relapse.

Engraftment was associated with a higher WBC count (p=0.01) but, most striking was the correlation of engraftment with cytogenetic risk group.

Xenografts were generated in only 4/30 patients (13%) with favourable karyotypes, 63/153 patients (41%) with intermediate-risk karyotype and 23/43 patients (53%) with adverse karyotypes (p=0.002). Furthermore, in normal karyotype AML patients, FLT3-ITD-positive patients established xenografts in 50% of samples compared to 27% of FLT3-ITD-negative cases (p=0.04).

Clinical outcome was shown to be closely correlated with ability to generate xenografts with only ~50% of patients entering complete remission if their samples produced engraftment compared with 80% of patients with non-engrafting samples ($p < 0.0001$). This resulted in a difference in both event-free and overall survival between the two groups ($p \leq 0.0001$).

Dr. James Kennedy, LEFT, University of Toronto, accepts the 2013 John H. Crookston Award at the 2013 CHS Annual Awards Dinner in New Orleans. Presenting the award is CHS Past-President, Dr. Stephen Couban, who completed his two-year term as President at the meeting, immediately preceding the 2013 Awards Dinner, December 7, 2013 in New Orleans. Looking on is Dr. Molly Warner, Secretary-Treasurer of the CHS.

The authors have convincingly demonstrated that the ability to engraft NOD.SCID mice with cells from an AML patient does correlate with clinical outcome. However, further work is needed to provide insight into the underlying determinants of this engraftment ability and to clarify if the engraftment behaviour is truly an independent prognostic indicator in AML. -ed.

CHS 2013 RESEARCH AWARD WINNERS

Residents & Fellows Category

Normal range of bleeding scores for the ISTH-BAT: adult and pediatric data from the merging project

- **Dr. Malak Elbatarny**
- **Queens University, Kingston, ON**
- **Supervisor: Dr. Paula James**

Dr. Malak Elbatarny

Standarized quantitative bleeding assessment tools (BATs) are utilized to report hemorrhagic symptoms and the International Society on Thrombosis and Hemostasis (ISTH) assessment tool (ISTH-BAT) was introduced in 2010 to consolidate and optimize previously described BATs, including the Vicenza Bleeding Questionnaire.

However, the normal ranges of the ISTH-BAT have not been determined and this study sought to establish the normal range for this tool in both adult and pediatric patients.

The investigators compiled bleeding score data from different studies that utilized Vicenza-based BATs using a specifically created bioinformatics system. The proposed normal ranges were then determined by removing outliers (> 3 standard deviations from the mean) and then selecting the mid-95th percentile.

The authors analyzed demographic and bleeding score data on 1079 adult (mean age 43 years) and 343 pediatric (mean age 9 years) subjects.

Normal ranges for the ISTH-BAT were established as 0-4 in adults and 0-2 for children less than age 18 years of age.

This study definitively established normal ranges for the ISTH-BAT, a critical step in objectively assessing bleeding symptoms. This should aid researchers in investigating the correlation between bleeding symptoms and genotypic, molecular and environmental data. -ed.

PhD and Post-Doctoral Category

Genomic rearrangements involving programmed death ligands are recurrent in primary mediastinal large B-cell lymphoma

- **David Twa, MSc**
- **British Columbia Cancer Agency, Vancouver, BC**
- **Supervisor: Dr. Christian Steidl**

David Twa

Primary mediastinal large B-cell lymphoma (PMBCL) is an aggressive malignancy typically seen in young woman.

Analysis of genomes and transcriptomes have highlighted inactivating mutations of TP53, amplification of chromosome 9p and chromosomal translocations involving CIITA as being linked to the pathogenesis of PMBCL.

The researchers decided to explore the link between two programmed death ligands located at 9p24.1, PDL1 and PDL2, and PMBCL. They performed break-apart FISH analysis on 551 clinical samples [125 PMBCL patients, 134 nodal diffuse large cell lymphoma patients (DLBCL), 130 primary CNS DLBCL patients, 82 testicular DLBCL and 80 other lymphoma patients] and 20 established cell lines. FISH analysis revealed that 20% of the PMBCL samples were positive for one of the two PDL genes, significantly more than in any other lymphoma ($p < 0.05$).

This compared with 1% in CNS DLBCL, 3% in nodal DLBCL and 7% in testicular DLBCL; none of the other lymphomas were positive for a PDL FISH abnormality.

Further analysis revealed PDL locus amplification in 45/125 (36%) of PMBCL samples.

Following analysis of whole genome and whole RNA transciptome libraries, the authors were able to characterize four novel fusion transcripts involving 9p24.1 locus found in one clinical case and three PMBCL cell lines.

This interesting study suggests that rearrangements involving the PDL locus are recurrent and relatively unique to PMBCL, leading to overexpression of PDL transcripts. This may well provide a therapeutic avenue to explore in this particular malignancy. -ed.

CHS 2013 RESEARCH AWARD WINNERS

PhD and Post-Doctoral Category

Determining cell-of-origin subtypes in diffuse large B-cell lymphoma using gene expression profiling on formalin-fixed paraffin-embedded tissue – an L.L.M.P.P. project

- **Dr. David Scott**
- **British Columbia Cancer Agency, Vancouver, BC**
- **Supervisor: Dr. Randy Gascoyne**

The cell-of-origin (COO) can separate diffuse large B-cell lymphoma (DLBCL) into germinal centre B cell (GCB) and activated B cell (ABC) subtypes based upon molecular characteristics.

With new therapeutic agents being developed with selective activity against GCB and ABC DLBCL, this study sought to create a robust and accurate molecular gene expression profile (GEP) assay (using a NanoString technology 20 gene assay) that could be applied to formalin-fixed paraffin-embedded tissue (FFPET). The investigators examined 119 cases of DLBCL (51 in a training cohort and 68 in a validation cohort) that had previously had COO assigned by gold-standard frozen-GEP analysis; all but 3 samples provided gene expression data of sufficient quality. COO was assigned in parallel at two different sites, the BCCA in Vancouver, BC and the NCI in Frederick, Maryland and showed 98% concordance.

Dr. David Scott

The COO for all gold-standard GCB cases was 100% concordant when tested with NanoString on FFPET. ACB DLBCL samples were correctly assigned in 93% of cases using the same NanoString technology.

This study demonstrates that accurate and rapid classification of COO is possible for DLBCL cases at diagnosis using routinely obtained FFPET. The value of this testing will depend upon the development of COO-specific therapy in DLBCL. -ed.

Junior Faculty Category

Epidemiology of post-transplant lymphoproliferative disorders following solid organ transplant in a major Canadian transplant centre

- **Dr. Anthea Peters**
- **University of Alberta, Edmonton, AB**

Post-transplant lymphoproliferative disorder (PTLD) can be a serious early or late complication in patients that undergo solid organ transplantation (SOT).

This project involved the review of over 4500 patients that underwent SOT between 1984 and 2011 and identified 133 cases of PTLD.

The PTLD cohort included 61 cases that were classified as "early" (< 2 years after SOT), 31 cases as "late" (2-7 years after SOT) and 39 cases as "very late" (> 7 years after SOT).

The cumulative incidence of PTLD was 2.6% at 5 years, 4.3% at 10 years and 7.9% at 20 years. Patients aged 0-5 years had the highest risk of early PTLD, perhaps because there was an increased risk of early PTLD in EBV-negative recipients receiving organs from EBV-positive donors.

Dr. Anthea Peters

Furthermore, the highest risk of early PTLD was in patients transplanted between 1984 and 1991 and the lowest risk in patients transplanted in the last decade of the study.

Multivisceral SOT and lung transplantation conferred the highest risk of PTLD, particularly late PTLD, and kidney transplant recipients had the lowest risk of any PTLD.

This study provides an excellent retrospective overview of PTLD in the SOT setting. The cumulative incidence of PTLD is significant following SOT although it is decreasing with time and is dependent upon recipient age, EBV serostatus and organ transplanted. -ed.

History Corner **Robert L. Noble and E. Clark Noble**

Noble brothers legacy a major contribution to hematology

Robert L. Noble and **E. Clark Noble** were brothers born into a prominent medical family, Robert (b. February 3, 1910), 10 years junior to Clark (b. December 29, 1900).

Their father, Robert T. Noble, was a GP who served as president of the Ontario Medical Association, the Canadian Medical Association, the College of Physicians and Surgeons of Ontario and the Medical Council of Canada. Clark Noble entered University of Toronto in 1918, majoring in physiology and biochemistry. He would go on to medical school and graduated with honours in 1925.

A brush with fame

However, he had his first brush with fame that began with his undergraduate classmate and best friend, **Charles Best**, and both were talented semi-pro baseball players.

Clark Noble and Charles Best began work as summer students in **J. J. R. MacLeod's laboratory in 1921** and were joined by a young surgeon, **Frederick Banting**. It was decided (by a coin toss!) that Best would assist Banting for the first month and Noble for the second.

In an experiment that Macleod was skeptical about in the first place, Banting and Best performed canine pancreatectomies, made extracts, injected them into diabetic dogs and measured blood glucose levels.

Dr. **J.B. Collip** was brought in to help purify the extracts but left in a dispute with Banting. Clark Noble's month of assistance never came to be and Best was subsequently put in charge of insulin production in Toronto. Nevertheless, Clark Noble's laboratory efforts contributed to the rapid increase in knowledge about insulin in the months after its discovery and co-authored 10 early papers on this hormone between 1922 and 1925.

In October 1923, Banting and, somewhat ironically, J. J. R. MacLeod were awarded the Noble Prize for the discovery of insulin.

Clark Noble went on to spend the summer of 1923 evaluating the feasibility of using fish as a commercial source of insulin.

He did extensive work in the cod fish industry but ultimately, evidence began to accumulate that large-scale production of fish insulin was impractical.

Charles Best and Clark Noble disagreed on this point and, not surprisingly, the former had a long and distinguished career in medical research while the latter became a GP in Toronto.

Major contribution to hematology

It was a result of his ongoing interest in diabetes that led to Clark and his brother Robert to make a major contribution in the field of hematology.

In 1952, a patient of Clark Noble's visited Jamaica and collected 25 leaves from the Madagascar periwinkle plant (*Vinca rosea*), which was commonly made into a tea to treat patients with diabetes, and sent it to him in an envelope. Clark was no longer involved in research and had no facilities to test the leaves for medicinal value so, he sent the envelope to his brother, Robert.

Robert L. Noble graduated from University of Toronto Medical School in 1934 before pursuing a PhD at the University of London in England.

In another twist of irony, he returned to Canada in 1937 and began to work with Dr. **J. B. Collip** who, by now, was studying endocrine-related cancers at McGill University.

In 1947, he became the **Associate Director of the Collip Medical Research Institute at the University of Western Ontario**.

With the arrival of the envelope of leaves sent by his brother Clark, Robert began studying the effects of the leaf extracts on blood glucose levels.

It turned out that the leaf extracts had little effect on glucose levels but did have inhibitory effects on white blood cells and the bone marrow.

Vinblastine isolated and purified

In 1954, **Charles T. Beer**, an organic chemist, joined Robert Noble's research team and together they isolated and purified a potent alkaloid extract in 1958 that they called "Vinblastine".

The team worked with Eli Lilly Co. to develop a small supply of Vinblastine for clinical trials, with the first occurring at Princess Margaret Hospital in Toronto in 1959.

Vinblastine and a related vinca alkaloid, Vincristine, both went on to become mainstays of chemotherapy in a number of different cancers, especially lymphoblastic leukemia and lymphoma.

Dr. Robert L. Noble

In honour of this ground-breaking discovery, The National Cancer Institute of Canada subsequently named its most prestigious award for excellence in research the **Robert L. Noble Prize**.

Robert L. Noble became the **Director of Cancer Research and Professor of Physiology at the University of British Columbia in 1960**. He was a skilled experimentalist and his research generated more than 200 publications.

He retired in 1975 but continued his research as an honorary member of the Division of Cancer Endocrinology at the BC Cancer Agency until his death on December 11, 1990. **In 1997, Dr. Robert L. Noble was inducted into The Canadian Medical Hall of Fame along with Dr. Charles Beer.**

Dr. E. Clark Noble continued his interest in fish insulin and was interviewed by the Toronto Star in 1974 during an impending insulin shortage. Despite his assurances, "*...we've done all the work on it and its already to go, if anyone is interested...*", commercial supply of fish insulin never came to pass.

Dr. E. Clark Noble died on May 18, 1978 and while there was no mention of his passing in the CMAJ at the time, an article did appear on his life and brushes with fame in December 2002.[1]

[1] *Wright J.R. Almost famous: E. Clark Noble, the common thread in the discovery of insulin and vinblastine. CMAJ 167:1391-1396, 2002.*

Mini Review

Lymphedema in the Context of Bone Marrow Failure

Dr. Thomas Nevill, Professor

University of British Columbia
Vancouver, BC

A 32-year-old woman is referred with a mild, non-progressive pancytopenia first identified at age 14 when she presented with idiopathic lymphedema of the left lower extremity.

She had three bone marrow examinations over the subsequent two decades which showed increasingly prominent trilineage dysplasia but no increase in blast cells and a normal female karyotype.

She reports a several year history of severe warts on her hands and feet as well as frequent respiratory tract infections.

Current blood work reveals a mild neutropenia an absolute lymphopenia and monocytopenia.

Dr. Thomas Nevill

An association between myeloid malignancy and idiopathic lymphedema was first observed by Emberger in 1979,[1] although a pathogenetic link was initially elusive. Not surprisingly, progress in molecular genetics provided the impetus that has led to a better understanding of the connection between these two uncommon disorders.

The GATA gene family is a group of six zinc finger-containing transcription factors found in multiple tissues. GATA1, GATA2 and GATA3 are primarily expressed in hematopoietic tissue and are lineage specific; GATA1 is expressed in erythroid cells, eosinophils and megakaryocytes and GATA3 is expressed in T-cells.[2] GATA1 has been linked to hematologic disease and mutations of this gene are seen in acute megakaryocytic leukemia and the transient myeloproliferation seen in Down syndrome.[3]

GATA2 (short for GATA-2 binding protein) is expressed in hematopoietic stem cells and myeloid progenitors and plays a critical role in their differentiation as well as in the regulation of tissue and alveolar macrophages.[2] Murine experiments show that GATA2 mutations, when homozygous, are fatal during gestation and, when heterozygous, induce stem cell apoptosis thereby reducing absolute stem cell numbers.[4]

The GATA2 gene is located at 3q21.3 and its protein product consists of two DNA-binding zinc finger domains (ZF) and four flanking sequences [two transactivation domains (TAD), a nuclear localization signal (NLS) and a negative regulatory domain (NRD)] (Figure 1).[5]

GATA2 mutations were first shown to play a role in hematologic disease in a CML patient with blast phase transformation.[6]

The key breakthrough in the linking of GATA2 mutations to hematologic disorders was an abstract presented at the American Society of Hematology Annual Meeting in 2010. This paper described four families with autosomal

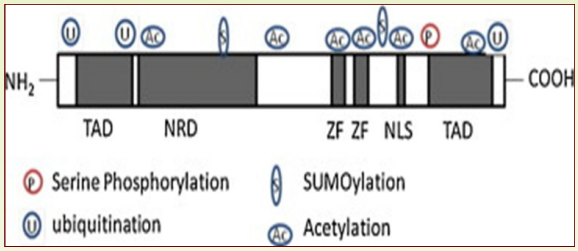


Figure 1. GATA2 protein structure

dominant MDS/AML that were shown to have mutations in the second zinc finger of the GATA2 gene.[7] This report followed on a publication earlier that year from the National Institutes of Health in Bethesda, MD describing a novel condition, MonoMAC syndrome, an autosomal dominant and sporadic monocytopenia with a predisposition to papillomavirus, fungal and non-tuberculous mycobacterial infections.[8] Researchers at the NIH, who were searching for a causative gene, were intrigued by the Scott abstract and began examining their patient cohort for GATA2 mutations. They quickly identified that all of those affected with MonoMAC syndrome had N-terminal mutations around the two zinc fingers leading to premature termination of GATA2 gene translation.[9]

As this exciting new work was unfolding in North America, the UK Lymphoedema Consortium was making progress of their own in understanding the link between MDS and lymphedema by describing 7 new cases of autosomal dominant AML with lymphedema ("Emberger syndrome").[10] These case had some common and interesting features – close set eyes, epicanthic folds, web neck, long tapering fingers, preceding MDS (often with monosomy 7), recurrent cellulitis in the affected limb and generalized warts. Concurrent with the discovery of GATA2 mutations as underlying MonoMAC syndrome was a publication from the Consortium clearly linking the AML/lymphedema disorder with similar GATA2 mutations.[11]

The publication of these two seminal papers in September 2011 led to a better understanding of the spectrum of diseases that can be linked to GATA2 mutations, shown diagrammatically in Figure 2. It is now clear that GATA2 mutations may manifest as recurrent non-TB mycobacterial/fungal infections (due to the monocytopenia) associated with sinopulmonary bacterial infections/alveolar proteinosis (due to alveolar/tissue macrophage dysfunction) – the MonoMAC phenotype.[8] However, these same identical mutations may produce Emberger syndrome (lymphedema, cellulitis and panniculitis), dendritic cell-monocyte-B/NK lymphoid ("DCML") deficiency syndrome (papillomavirus and EBV infections with associated anogenital malignancies), familial MDS/AML (without any other associated manifestations), all with considerable potential for overlap, and even an apparently normal phenotype.[12] The common hematologic link for

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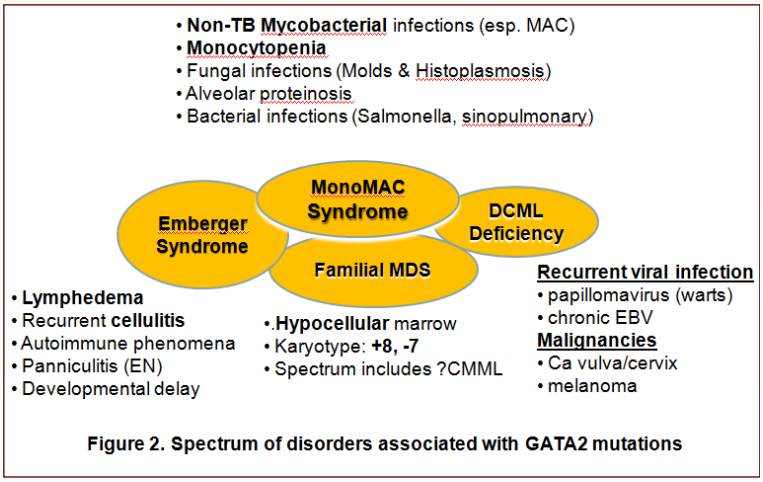

Figure 2. Spectrum of disorders associated with GATA2 mutations

Ask the Hematologist

A new case of chronic myeloid leukemia

Dr. Brian Leber, Professor
McMaster University, Hamilton, ON
and
Dr. Christopher Hillis, Hematology
Fellow, McMaster University

A 58-year-old man presents with a 3 month history of fatigue, night sweats and left upper quadrant pain.

He has a history of having had a myocardial infarction 5 years previously at which point he was found to have hypertension and hypercholesterolemia.

His CBC shows a Hemoglobin of 102 g/L, WBC of 156 x 10e9/L with a left shift including 2% blasts and a platelet count of 769 x 10e9/L.

Physical examination reveals a spleen that is 8 cm below the left costal margin.

Bone marrow examination shows 100% cellularity with eosinophilia, 9% basophils and 3% blast cells.

Cytogenetics reveal t(9;22) in all 50 metaphases analyzed.

How should this patient be managed?

CML is a rare disease with an incidence of 1-2 cases per 100,000 people per year. It is characterized by the obligatory presence of a reciprocal chromosomal translocation t(9;22)(q34;11) that leads to fusion of the ABL gene from chromosome 9 and the BCR gene from chromosome 22. The resulting Philadelphia chromosome (Ph) produces the BCR-ABL1 fusion protein with dysregulated tyrosine kinase activity mediating the leukemic phenotype.

The diagnosis of CML is confirmed by cytogenetically identifying the Ph chromosome in the bone marrow; potentially along with other karyotypic abnormalities that may have prognostic significance. Staging (phase) is based on blast percentage in the blood and marrow, degree of basophilia, platelet count, and presence of extramedullary blast proliferation. Patients are diagnosed as chronic phase (CP), accelerated phase or blast phase. Prognosis is largely determined by stage; however, in chronic phase prognostic information is

Dr. Christopher Hillis, Hematology
Fellow, McMaster University

determined by clinical scoring systems (i.e. Sokal, Hasford, and EUTOS). The EUTOS score is based on prognosis with imatinib therapy and is appropriate for this context to

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this spectrum of diseases is bone marrow failure with a predisposition to develop hypocellular MDS/AML with monosomy 7 or trisomy 8 (although even chronic myelomoncytic leukemia has been seen in patients with GATA2 mutations).[12]

Following the description of the GATA2 mutation-related disease spectrum, subsequent research has focused on treatment and attempting to understand how GATA2 mutations produce both a predisposition to MDS/AML and unusual infections as well as lymphedema.

There has been considerable progress in the area of treatment, with prevention of infection through prophylaxis and immunization and the use of stem cell transplantation to treat the associated bone marrow failure.[13]

There have also been important developments in understanding the pathogenesis of the lymphedema and MDS/AML combination. An abnormality in vascular endothelial growth factor (VEGF) has long been suspected as a unifying concept that could explain the Emberger syndrome phenotype.

A recently published study involving 78 patients with autosomal recessive or dominant familial lymphedema supports this suspected link.[14] These investigators found that 36% of familial lymphedema patients had a mutation in one of five genes involved in the VEGFR3 signalling pathway. The mutated genes included FLT4 (the gene actually encoding the transmembrane receptor, VEGFR3), as well as GATA2, FOXC2, SOX18, CCBE1 and GJC2. The signalling pathway and the genes and protein products potentially affected are shown in Figure 3.

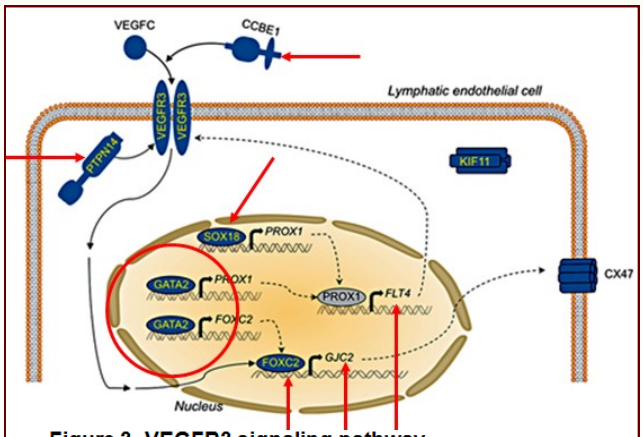

Figure 3. VEGFR3 signaling pathway

GATA2 mutations appear to play an important role in the pathogenesis of a number of overlapping clinical syndromes characterized by predisposition to MDS/AML, lymphedema and recurrent infections.

Evidence is accumulating that GATA2 mutations lead to a disturbance in the VEGFR3 signalling pathway, resulting in both bone marrow failure and lymphatic endothelial cell dysfunction.

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determine risk; however the two older scores have been widely used to assign risk in all major clinical trials to date. This patient has CP CML with a Sokal score of 1.35 (high risk) and a EUTOS score of 95.

Treatment guidelines recommend first-line therapy with 1 of 3 approved tyrosine-kinase inhibitors (TKIs). While awaiting a diagnosis hydroxyurea may be used for cytoreduction. Deciding which TKI is most appropriate for our patient requires balancing disease characteristics and patient comorbidities as they relate to the drugs' safety profiles. Imatinib has been available for over a decade and long term reports demonstrate a PFS of 83%-94% at more than 5 years, however, only 50% of patients remain on imatinib treatment after 8 years. The second generation TKIs (2G TKI; dasatinib and nilotinib) have been compared prospectively frontline to imatinib and show superiority in rate and depth of milestone response.

Disease characteristics that warrant consideration for frontline therapy include high Sokal risk, the presence of major route cytogenetic abnormalities in the +Ph clone (+8, i[17q], +19, -Y, +21, +17, and -7) and the rare patient who presents with p190 (e1a2 rearrangement). Additional cytogenetic abnormalities (ACA) have a variable impact on survival and appear in approximately 5% of cases of at diagnosis. For these patients and patents with p190 there are reports of reduced effectiveness of imatinib and this warrants consideration of a 2G TKI initially. The ELN guidelines recommend HLA typing of patients and siblings with baseline warnings including high risk Sokal or major route cytogenetic abnormalities.

Each TKI has a unique safety and tolerability profile. Major side effects which typically occur on treatment initiation result in discontinuation in approximately 10% of patients. Minor side effects can begin early in treatment and if persist, effect tolerability and potentially compliance. These are typically not unique to individual TKIs but differ in frequency and severity. Off-target complications may occur later in the course of therapy and can affect multiple systems (i.e. cardiovascular, endocrine, hepatic, etc…). All TKIs are cardiotoxic. The late off-target complications need to be taken into consideration when selecting firstline therapy for our patient.

Dasatinib has been associated with pleural and lung complications. The incidence of pleural effusions is approximately 20%. Notably, dasatinib may increase the risk of pulmonary arterial hypertension. Nilotinib has been associated with arterial pathology.

Dr. Brian Leber, Professor
McMaster University, Hamilton, ON

Related to our patient there are concerns over increased arterial disease risk (both peripheral and coronary) potentially mediated or exacerbated by observed elevations in cholesterol and glucose while on nilotinib. We must assess our patient's risk for arterial disease prior to initiating therapy and obtain baseline cholesterol and glucose levels. If peripheral arterial occlusive disease is confirmed prior to or during therapy, nilotinib should be avoided. Choosing one of the 2G TKIs in our patient requires initial and ongoing cardiopulmonary and cardiovascular evaluations.

High Sokal risk may be an indication for choosing a 2G TKI frontline although this is still an active area of discussion among various international co-operative groups. Given this patient's disease characteristics close follow-up and molecular monitoring (with quantitative RT-PCR) according to the most recent guidelines is essential. It is clear that the molecular response at 3 months predicts long-term outcomes. CP patients who fail to achieve a BCR-ABL <10% by 3 months have a risk of progression of greater than 10%. What is not known is whether switching to an alternative TKI in patients who fail this milestone will decrease the risk. There is no published prospective data that directly addresses this strategy.

Our practice, despite lack of a formal guideline or expert consensus recommendation, would be to start this patient on a 2G TKI. The choice of agent based upon a thorough assessment of his comorbidities. Other practitioners may opt for imatinib and reserve a 2G TKI for salvage. Either approach is reasonable at this time until further information on the prospective management of high risk patients is available.

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CHS Participates — Choosing Wisely Canada

Choosing Wisely Canada (CWC) is a campaign to help physicians and patients engage in conversations about unnecessary tests, treatments and procedures and support physician efforts to help patients make smart and effective choices to ensure high quality care.

This past winter we announced that the CHS will be participating in the campaign.

CWC is modeled after the hugely successful ***Choosing Wisely***® campaign in the United States. Initiated and coordinated by the ABIM Foundation, 60 medical societies have to date joined the campaign to develop "***Top 5 Lists***" of tests and treatments physicians and patients should question – things for which there is strong evidence of overuse, waste, or even harm to patients.

The first eight Canadian medical societies have compiled their lists and they will be presented this April.

ASH presented their list this past December sparking lively debate and interest. We look forward to coming together as a society and developing a Canadian version of this list.

Please watch for communication from the CHS about this initiative and your opportunities to be involved.

Choosing Wisely Canada

Any questions or comments please contact Chris Hillis (hillisc@mcmaster.ca).

Hicks LK et al. The ASH Choosing Wisely Campaign: Five hematologic tests and treatments to question. Blood 2013 Dec 5; 122:3879.

Please join us, June 13, 2014, Halifax, Nova Scotia!

CHSCH

This is a joint meeting with

- The Canadian Apheresis Group (CAG), and
- The Canadian Blood and Marrow Transplant Group (CBMTG)

This general hematology day will be of interest to:

- Hematologists
- Internists
- Family physicians with an interest in hematology
- Others with a general interest in hematology

You will not be charged a fee but it is important that you **Please REGISTER**

To register, RSVP by email to: **chsincanada@gmail.com** with the following 3 details:

1. Your name _____
2. Your institution _____
3. Whether or not you will be joining us for lunch _____

Upcoming Events — Mark your calendar - Save the date!

Canadian Hematology Society
Friday, June 13, 2014
Halifax, Nova Scotia **Contact**: chs@uniserve.com

This is a joint Canadian meeting with CAG, CAAN and CBMTG:

- **The Canadian Apheresis Group (CAG)**
  &
  The Canadian Association of Apheresis Nurses (CAAN)
  Annual General Meeting and Scientific Sessions
  June 13—15, 2014
  Halifax, Nova Scotia **Contact**: cag@cagcanada.ca

- **Canadian Blood and Marrow Transplant Group Annual Conference (CBMTG)**
  June 11—14, 2014
  Halifax, Nova Scotia **Contact**: www.cbmtg.org

International Society for Hematology and Stem Cells (ISEH)
43rd Annual Scientific Meeting
August 21-24 2014
Hyatt Regency, Montreal
http://www.iseh.org/?2014Montreal

CHS Annual Reception, Dinner & Awards Evening
Sunday, December 7, 2014
San Francisco
Contact: **chs@uniserve.com**

International Society of Thrombosis and Haemostasis (ISTH)
25th World Congress
July 11—17, 2015, Toronto, Ontario Contact: https://www.isth.org

Invitation to submit ...

The Microenvironment **will be happy to consider for publication, articles submitted by members who have sponsored student summer projects.**

Queries should be directed to:

- **Dr. Tom Nevill, The Editor, *The Microenvironment***
- **Email: chs@uniserve.com**

STUDENT RESEARCH ARTICLES

Fellowships

Boris Family Fellowships in Stem Cell Hematology McMaster University

- Specific focus on blood stem cells.
- Positions are for up to three years. Fellows will gain experience in the application of stem cell biology, as it relates to treatment of blood disorders, and will have the opportunity to undertake clinical activities.
- The starting date for appointments is negotiable, but is anticipated to be July 2014. Candidates must have completed subspecialty training in medical oncology or hematology and be eligible for licensure with the College of Physicians and Surgeons of Ontario.
- Candidates should submit a detailed statement of interest and CV and arrange for 3 letters of reference to be sent by the application deadline. Applications received by March 31, 2014 will be assured of consideration.
- Enquires and applications:

Administrative Manager
Boris Family Gift
Faculty of Health Sciences
Michael G. DeGroote School of Medicine
McMaster University
1280 Main Street West
Hamilton, ON, L8S 4K1
care of:
liddell@mcmaster.ca

The Alexandra Yeo Fellowship in Thrombosis and Hemostasis

- Two year academic combined fellowship program in thrombosis and hemostasis.
- This program offers a unique clinical exposure in arterial and venous thrombosis, hemophilia and other inherited coagulation factor deficiencies, platelet disorders, and coagulation laboratory diagnosis.
- The fellow is expected to enrol in a funded Master's course if not previously undertaken postgraduate studies. This should be in alignment with their academic focus, i.e. clinical epidemiology/health research methodology, medical education, public health, or quality improvement.
- Interested residents should submit their CV, including 3 named referees, with covering personal statement by email to:

richard.ward@uhn.ca
by February 28th 2014 for a start date of July 1, 2014.
Any enquiries may be directed to
Dr. Richard Ward, Benign Hematology

University Health Network

Medicine UNIVERSITY OF TORONTO
SickKids St. Michael's Sunnybrook UHN

...from Page 4 :

The DIAGNOSIS? Answer:

The peripheral blood showed a leukoerythroblastic picture with 60% eosinophils and 10% blast cells.

The bone marrow was a dry tap with touch preparation and biopsy showing complete marrow replacement with malignant cells, ranging in appearance from microblasts to large undifferentiated cells, along with prominent eosinophilia.

Lymph node biopsy showed replacement by a similar malignant cell population that were CD45, CD117, CD56, CD5, CD7 and CD38-positive but negative for CD3, TdT and CD123; TcR gene rearrangement was positive. CD3 negativity ruled out T-LBL and CD123 negativity ruled out blastic plasmacytoid dendritic cell neoplasm ("blastic NK cell lymphoma"). Despite the clinical and pathologic features being suspicious for an FGFR1 translocation, karyotype was normal female.

She was treated with Cyclophosphamide and Prednisone; after her hepatic function had improved, Doxorubicin, Vincristine and L-Asparaginase were added. She entered complete remission, had a matched sibling identified and was successfully consolidated with allogeneic stem cell transplantation.

Fellowships

Thrombosis Fellowship 2012-2013 Jewish General Hospital, McGill University

The JGH Thrombosis Program is currently accepting applications for a one year fellowship (July 1, 2014—June 30, 2015) to acquire and consolidate expertise in Thrombosis. Specific areas of clinical activity include the Thrombosis Clinic, Anticoagulation Clinic and In-patient Thrombosis Consultation Service. Our Thrombosis Program also encompasses a broad range of research activities that relate to diagnosis, risk factors and treatment of venous and arterial thromboembolic disease.

Jewish General Hospital

For information, please contact:

Dr. Susan Kahn
514-340-7587
susan.kahn@mcgill.ca

Thrombosis Clinical & Research Fellowships - Up to 3 positions

Applications are encouraged from MDs who have completed or who will complete General Internal Medicine, Respirology and/or Hematology training. Foreign medical graduates with equivalent qualifications are eligible.

Applicants may apply to one of three training streams:
1.) Clinical Fellowship, one-year—To consolidate expertise in thrombosis.
2.) Clinical and Research Fellowship, 2-3 years (to become a clinician investigator in thrombosis (Fellows enroll in the Master's of Clinical Epidemiology Program at the University of Ottawa).
3.) Clinical and Education Fellowship, 2-3 years (to become a clinician educator in Thrombosis. (Fellows enroll in a Master's in Education).

THE OTTAWA HOSPITAL
L'HÔPITAL D'OTTAWA

To apply, please contact:
nlanglois@ohri.ca

Details are also available on the CHS website.

LEUKEMIA/BONE MARROW TRANSPLANTATION FELLOWSHIP VANCOUVER

The Leukemia/Bone Marrow Transplantation Program of British Columbia offers 1 or 2 Year fellowships to provide advanced training in the management of adults with hematological malignancies including all aspects of allogeneic and autologous hematopoietic stem cell transplantation (HSCT).
Candidates should be registered in, or completed a recognized hematology or oncology training program.
For more information: leukemiabmtprogram.org
Interested candidates should submit
a CV and names of three references to:
Dr. Donna Forrest, Fellowship Director,
Leukemia/BMT Program
BC Cancer Agency & Vancouver General Hospital

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

Phone: (604) 875-4089
FAX: (604) 875-4763
Email: dforrest@bccancer.bc.ca

The Microenvironment

March 2014

Your Canadian Hematology Society
Société Canadienne d' Hématologie Newsletter

Membership Matters

The Canadian Hematology Society has represented all physicians and scientists with an interest in the discipline in Canada since it was founded in 1971, and currently has over 400 members.

Active Membership

- Physicians in the practice of clinical or laboratory hematology in Canada
- Scientists with PhD degrees making continuing contributions to research related to hematology in Canada
- Allied Health Professionals with university degrees making sustained contributions to clinical or laboratory hematology practice or hematology research in Canada.

Only active members shall:

- **vote**
- **hold office**
- **receive CHS grants, and**
- **pay dues.**

Associate Members

- Residents and fellows engaged in hematology training
- Masters and PhD graduate students
- Post-doctoral fellows engaged in hematology research

Associate members will not be required to pay dues until completion of their training.

Emeritus Members

- All individuals who have retired from full time hematology practice or research, or those who were active members and request a transfer of status with adequate reason.

Honorary Membership

- Non-members may be invited to become Honorary Members of the corporation by virtue of their outstanding contributions to any discipline which is of importance to hematology.

CHS members are reminded … that dues for the year 2014, were due on January 1, 2014.

Your $75. annual dues payment may be made online at the CHS website:
www.canadianhematologysociety.org

Or by mail to: **Canadian Hematology Society, 199-435 St. Laurent Blvd., Ottawa, Ontario K1K 2Z8**
Please provide the following information with your payment:

2013 Membership Renewal: Canadian Hematology Society

Membership Status

Active ☐
Associate ☐
Emeritus ☐

Has your status changed?

Yes ☐
No ☐

Name: _____

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